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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte RANDOLPH J. NOELLE, TERESA M. FOY, and
FIONA H. DURIE

Appeal 2009-003956
Application 09/164,568
Technology Center 1600

Decided: September 24, 2009

Before RICHARD M. LEBOVITZ, FRANCISCO C. PRATS, and
JEFFREY N. FREDMAN, *Administrative Patent Judges*.

LEBOVITZ, *Administrative Patent Judge*.

DECISION ON APPEAL

This is a decision on the appeal by the patent applicants from the patent Examiner's rejection of claims 82-94 under 35 U.S.C. 103(a). The Board's jurisdiction for this appeal is under 35 U.S.C. § 6(b). We reverse.

STATEMENT OF THE CASE

The claims are to methods “for reducing antigen-specific T cell responsiveness *in vivo*” comprising administering (a) an antigen presenting cell (“APC”) expressing an autoantigen; and (b) an anti-gp39 antibody. Gp39 is a ligand for CD40, a protein found on the surface of B cells (Spec. 2:23-29). Gp39 is expressed on activated, but not resting T cells (*id.* at 2:30-31). The gp39 protein, when expressed on the T cell surface, can trigger B cell proliferation and antibody production (*id.* at 2:33-36). The Specification states that

it has been discovered that, under appropriate conditions, interference of an interaction between gp39 on a T cell and a ligand on a cell which is presenting antigen to the T cell [an APC, such as a B cell] can induce antigen-specific T cell tolerance. Accordingly, the cell which presents antigen to the T cell requires an interaction between a gp39 ligand (e.g., CD40) on the cell and gp39 on the T cell to be able to provide signals necessary for activation of the T cell. Inhibition of the interaction between the gp39 ligand and gp39 [with an anti-gp39 antibody] prevents T cell activation and rather induces antigen-specific T cell tolerance.

(Spec. 3:7-14.)

All pending claims 82-94 stand rejected by the Examiner under 35 U.S.C. § 103(a) as obvious in view of Lederman (US 6,403,091 B1, Jun. 11, 2002), Beschorner (US 5,597,563, Jan. 28, 1997), Eynon (*Small B Cells as Antigen-presenting Cells in the Induction of Tolerance to Soluble Protein Antigens*, 175 J. EXP. MED. 131-138 (1992)), and Cobbold (US 5,690,933, Nov. 25, 1997) (Ans. 4).

Claim 82, the only independent claim on appeal, is representative and reads as follows:

82. A method for reducing antigen-specific T cell responsiveness *in vivo*, which method comprises administering to a subject in need of such treatment:

(a) an antigen-presenting cell that presents an autoantigen to an activated T cell expressing mouse or human gp39; and

(b) an anti-gp39 antibody which binds to mouse or human gp39 on the activated T cell,

wherein the anti-gp39 antibody is administered prior to, concurrent with, or subsequent to administration of the antigen-presenting cell in an amount effective to reduce T cell responsiveness to the antigen-presenting cell.

STATEMENT OF ISSUE

Claim 82 is directed to a method “for reducing antigen-specific T cell responsiveness *in vivo*” comprising administering (a) an APC expressing an autoantigen; and (b) an anti-gp39 antibody. Citing Beschorner and Eynon for teaching APC administration, Lederman for its teaching of an anti-gp39 antibody, and Cobbold for a combination of antigen and antibody, the Examiner concluded that the claimed invention would have been obvious to a person of ordinary skill in the art. Appellants contend that the Examiner erred in failing to cite references or general knowledge that would suggest or motivate the ordinary skilled worker to have combined the references to arrive at the claimed invention (App. Br. 10). The issue in this appeal is whether Appellants established that the Examiner erred in finding a reason to have combined the cited prior art.

PRINCIPLES OF LAW

A factfinder should be aware, of course, of the distortion caused by hindsight bias and must be cautious of arguments reliant upon *ex post* reasoning. *See Graham*, 383 U.S., at 36, 86 S.Ct 684 (warning against a “temptation to read into the prior art the

teachings of the invention in issue” and instructing courts to “‘guard against slipping into the use of hindsight’ ” (quoting *Monroe Auto Equipment Co. v. Heckethorn Mfg. & Supply Co.*, 332 F.2d 406, 412 (C.A.6 1964))). Rigid preventative rules that deny factfinders recourse to common sense, however, are neither necessary under our case law nor consistent with it. *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 421 (2007).

SCOPE AND CONTENT OF THE PRIOR ART

When making an obviousness determination, the scope and content of the prior art must first be ascertained. *Graham v. John Deere Co.*, 383 U.S. 1, 17 (1966). The following numbered facts (“F”) summarize the prior art relied upon the Examiner in setting forth the basis of the rejection.

The Lederman patent

1. Lederman teaches that resting T cells contact antigen primed B cells (or other APCs) resulting in the T cell becoming activated (col. 1, ll. 28-54). Activated T cells cause B cells to differentiate into antibody secreting cells (col. 1, ll. 35-42; col. 2, ll. 8-12; Spec. 1:17-36).
2. Lederman describes a monoclonal antibody, 5c8, which binds to the CD40 ligand located on the surface of activated T cells, thereby inhibiting “T cell activation of B cells.” (Col. 2, ll. 15-21.)
3. Lederman states that the antibody binds to T cells which are interacting with B cells in the lymph nodes, and does not bind to other T cells (col. 7, ll. 7-9). By binding to the CD40 ligand on the T cell surface, the antibody inhibits B cell activation (*id.* at 7:10-14).

4. Methods are described by Lederman of inhibiting the immune response of an animal by administering an effective amount of the antibody (col. 11, 8-40).
5. In one embodiment, Lederman teaches “inhibiting the autoimmune response in an animal suffering from autoimmune disease.” (Col. 11, ll. 40-49.)

The Beschorner patent

6. Beschorner describes its invention as a “method of inducing antigen-specific tolerance in an animal.” (Col. 4, ll. 35-36.) The “method entails treatment of an animal with an immunosuppressant agent under conditions sufficient to deplete the thymic medulla, or thymic equivalent, of antigen presenting cells, followed by infusion of dendritic cells which are tolerogenic for the antigen.” (Col. 4, ll. 36-41.)
7. The antigen to which tolerance is desired is displayed on the APC surface for presentation to the T cell (col. 6, ll. 49-65).
8. The immunosuppressive agent is defined by Beschorner as “an agent which depletes the thymic medulla of APCs, such as dendritic cells.” (Col. 8, ll. 1-3.)
9. The immunosuppressive agents induce depletion of APCs from the thymus (col. 8, ll. 31-33).

Physiologically, one role of these cells is to act in a “barrier-like” manner between the cortex and the medullary regions of the thymus. In this role, these cells prevent the transit of immature conical [sic, cortical] thymocytes from the cortex out of the thymus. However, upon depletion of the APCs from the medulla this barrier function becomes impaired and, as a result, cortical thymocytes appear in extra-thymic regions, such as the peripheral blood. Thus, it is possible to monitor the

effectiveness of an immunosuppressive agent of the invention simply, for example, by detecting the increase of immature thymocytes in the peripheral blood. (Col. 8, ll. 34-46.)

10. After the immunosuppressant is administered, the animal is infused with “donor dendritic cells [acting as APCs] . . . able to induce tolerance to donor antigens carried on the surface of the dendritic cell. The donor dendritic cells will re-populate the thymus of the recipient host and re-program the host T-cells to be tolerant of donor antigens of the donor” tissue (col. 8, ll. 55 to col. 9, l. 5).

Eynon

11. Eynon teaches that resting B cells, acting as antigen-presenting cells, are able to induce tolerance to soluble protein antigens in mice (Abstract).

12. Eynon proposes “that presentation of antigen by a small, resting B cell to a small resting T cell is tolerogenic and results in loss of T cell activity.” (P. 131, col. 2.)

13. Eynon does not administer the B cells to animals, but rather administers to mice a soluble protein antigen which is processed by B cells (p.132, 1st full paragraph; p. 135, “Discussion”). After antigen administration, the mice become tolerant to the antigen (*id.*).

The Cobbold patent

14. Cobbold describes producing tolerance in an animal by administering “non-depleting” CD4 and CD8 antibodies which reduce the population of certain T cells (Abstract; col. 1, l. 45 to col. 2, l. 66).

15. Antigen may be administered with the antibodies because “[p]ersistent [sic] antigen is required to maintain tolerance.” (Col. 3, ll. 56-60.)

“Tolerance can therefore be induced to an antigen in a host by administering

non-depleting CD4 and CD8 mAbs and, under cover of the mAbs, the antigen.” (Col. 3, ll. 44-46.)

CLAIM INTERPETATION

16. Claim 82 is to a method of reducing antigen-specific T cell responsiveness in vivo. The method comprises administering two components to a subject:

17. “(a) an antigen-presenting cell that presents an autoantigen to an activated T cell expressing mouse or human gp39; and”

18. “(b) an anti-gp39 antibody which binds to mouse or human gp39 on the activated T cell.”

19. An “autoantigen” would be understood by persons of ordinary skill in the art to mean a self-antigen which is a normal constituent of the subject’s body. (Beschoner, col. 5, ll. 51-57.) The Specification states that reducing T cell responsiveness to an autoantigen is useful for treating an autoimmune disease (Spec. 14: 1-3).

20. Gp39 is a protein expressed on the surface of T cells which acts as a ligand for the CD40 protein on B cells (Spec. 2:23-36; 3:2-14). Gp39 is also known as the CD40 ligand (*id.* at 2:27-28).

21. Claim 82 recites (a) an APC “that presents an autoantigen to an activated T cell” which expresses gp39. We interpret this to mean that the APC is “capable” of presenting the autoantigen to an activated T cell, and therefore T cell antigen presentation is a functional property of the APC. However, the claim does not positively recite a step in which the APC is administered to the activated T cell. Rather, the method comprises “administering to a subject” the APC component; it does not recite that the

APC is administered to an activated T cell or to a subject with activated T cells.

DIFFERENCES BETWEEN THE CLAIMED INVENTION AND THE PRIOR ART

Once the scope and contents of the prior art have been determined, the differences between the prior art and the claimed invention must be identified. *Graham*, 383 U.S. at 17. The following facts are relevant to this determination:

22. Lederman describes a method of inhibiting an autoimmune response by administering an antibody which binds to the CD40 ligand on the surface of activated cells (F1-2). The CD40 ligand is the same protein as gp39 (F20). Appellants do not dispute that Lederman's antibody meets the limitation of the claimed "(b) . . . anti-gp39 antibody."

23. Lederman does not disclose administering the (b) anti-gp39 antibody with "(a) an antigen-presenting cell that presents an autoantigen to an activated T cell expressing" gp39 as in claim 82.

24. Beschorner describes inducing tolerance with APCs (dendritic cells) that present a self antigen to T cells, along with an immunosuppressive agent (F6-10). Appellants do not dispute that Beschorner's APCs meet the claimed limitation of (a) "an antigen-presenting cell" that is able to present an autoantigen to an activated T cell.

25. Eynon teaches that resting B cells, acting as antigen-presenting cells, are able to induce tolerance to soluble protein antigens in a subject (F11-13).

26. Neither Beschorner nor Eynon describe administering the APC in combination with an anti-gp39 antibody as claimed in claim 82.

27. Cobbold describes administering antibodies to T cells and an autoantigen (F14-15), but not anti-gp39 and not autoantigen in the form of an APC.

REASON TO COMBINE THE PRIOR ART

Having established the differences between the prior art and the claimed invention, the next step is to identify a reason why persons of ordinary skill in the art would have been prompted to combine the prior art to have made the claimed invention. *KSR*, 550 U.S. at 418.

28. The Examiner found that Cobbold teaches antibodies directed to CD4-expressing T cells, which are the same T cell subpopulation targeted by Lederman's gp39 antibodies (Ans. 16).

29. The Examiner also found that Cobbold teaches administration of self-antigen to produce tolerance, but not as an APC (*id.*).

30. However, the Examiner found that "Beschorner teaches an alternative means (antigen-presenting cells) to provide persistent antigen, antigen reminders or antigen of interest at the time of administering immunosuppressive agents, such as immunosuppressive anti-T cell antibodies." (*Id.*)

31. The Examiner concluded that the ordinary skilled worker would have been motivated to select the combination of an autoantigen containing antigen presenting cells [the Beschorner APCs] and a gp39-specific antagonist [the Lederman antibody] to induce antigen-specific non-responsiveness to autoantigens as a treatment for autoimmunity by providing persistent autoantigens under the cover of immunosuppressives, since both contribute to long term antigen non-responsiveness in the treatment of autoimmunity.

(Ans. 6.)

ANALYSIS

The disputed issue in this appeal is whether persons of ordinary skill in the art would have had reason to combine Lederman's anti-gp39 antibodies with Beschorner's APCs to reduce antigen-specific T cell responsiveness as required by claim 1.

The Examiner found that while the claimed combination of an anti-gp39 antibody and autoantigen presenting APC was not disclosed in the prior art, both components were known to the ordinary skilled worker as evidenced by Lederman and Beschorner, respectively, and had been used to induce antigen tolerance (F4, 6, 22-24) and thus would have been obvious to combine (F31). The Examiner also found that an antibody/antigen combination had been taught by Cobbold as useful for inducing tolerance (F14, 15). Based on this teaching, the Examiner reasoned that it would have been obvious to have utilized Lederman's antibody in place of Cobbold's antibody, and Beschorner's antigen presenting cell in place of Cobbold's antigen in order to induce antigen tolerance (F28-31).

Appellants challenged the Examiner's case as lacking a reason to combine. They contend that the mechanisms and cell populations described in Lederman, Beschorner, and Cobbold differ and therefore there would have been no motivation to have combined the references. To resolve this dispute, we must turn to the facts.

Lederman described using a monoclonal antibody targeted against activated T cells to inhibit the immune response (F1-5). Lederman's antibody inhibited the B cell (acting as an APC) from activating the T cell (F2). In Beschorner, the T-cells are re-programmed "to be tolerant of donor antigens" by autoantigen presenting APCs (the same type as claimed)

administered after a step in which the host thymus is depleted of APCs (F6-10). Therefore, as argued by Appellants, Lederman and Beschorner utilized different approaches to achieve the same end of reducing T cell responsiveness: Lederman administered antibodies; Beschorner provided antigen presenting cells.

Moreover, in Beschorner's system, dendritic APCs are infused into the subject where they interact with and produce autoantigen tolerance in the subject's T cell population (F6, 7, & 10). On the other hand, Lederman's goal is inhibit the interaction between the APC and T cell populations (F2 & 3). The Examiner did not establish a reason to have utilized Lederman's inhibitory antibody in a system aimed at promoting the T cell/APC interaction.

Appellants also argue that different T cell populations were treated in Lederman and Beschorner, respectively. Appellants contend that Lederman targeted activated T cells, while Beschorner's target was immature T cells (App. Br. 6¹). According to Appellants, the thymus in Beschorner's subject was depleted of APCs (*id.*). T cells become activated by APCs (F1). Therefore, Appellants assert, T cell activation would have been prevented in Beschorner (App. Br. 6).

Appellants' argument is logical as to why T cell activation would be prevented by APC depletion. However, there is insufficient evidence that the subject in Beschorner would have been completely devoid of activated T

¹ Appellants also contend that the claims require administration of the anti-gp39 to an activated T cell. This interpretation is narrower than the claim language dictates. The claims do not require that the APC is administered to an activated T cell or a subject having activated T cells (F21).

cells immediately prior to or after APC administration. Nonetheless, Beschorner does not identify the specific class of T cells treated by its method nor did the Examiner establish that Beschorner targeted activated T cells. Therefore, we conclude that it would have been uncertain that Beschorner's treated T cell population was the same as Lederman's.

In view of the apparent differences between Beschorner and Lederman – in both mechanism and targeted T cell populations – we conclude that the ordinary skilled worker would not have had adequate reason to combine the references in the manner suggested by the Examiner.

Eynon was also cited by the Examiner as a reason to have utilized APCs in combination with an anti-gp39 antibody to reduce antigen-specific T cell responsiveness as recited in claim 82. However, although Eynon's investigation does ascribe tolerogenic activity to antigen-presenting B cells, Eynon did not induce tolerance by actually administering the APCs (F13). In contrast, Beschorner actually administered APCs to induce tolerance, but disclosed that doing so requires administration of an immunosuppressive agent to deplete the subject's thymic medulla of APCs (F6, 8).

Eynon also explicitly teaches that it treats a "resting T cell" (F12), not an activated T cell as in Lederman (F2-3). Thus, Eynon and Lederman were concerned with different T cell targets.

For these reasons, we are not persuaded that a person of ordinary skill in the art would have combined such a process with Lederman's method. Given Eynon's failure to describe inducing tolerance by administering APCs and its concern with a different cell population than taught in Lederman, we are not persuaded that Eynon bolsters the Examiner's posited combination of Lederman and Beschorner.

In sum, neither the teachings in Beschorner nor Eynon would have been combined with Lederman by persons of ordinary skill in the art. The Examiner appeared to have been guided by hindsight.

The Examiner also found it obvious to have substituted Cobbold's non-depleting antibodies for Lederman's anti gp39. Again, we do not find sufficient evidence to support the reasonableness of the combination. Cobbold's antibodies were to reduce a T cell population (F14). Lederman's were to directed to activated T cells to inhibit the T cell from activating B cells (F1). The prior art references were concerned with different antibodies, targeting not only different molecules (CD4/CD8 vs. gp39) but also having different effects on the cells (reducing the cell population vs. preventing an interaction) (App. Br. 12). Consequently, we discern no logical reason to have combined Lederman with Cobbold.

CONCLUSION OF LAW & SUMMARY

The Examiner erred in concluding that the method recited in claim 82 would have been obvious to persons of ordinary skill in the art in view of Lederman, Beschorner, Eynon, and Cobbold. The obviousness rejection of claim 82, and dependent claims 83-94, is reversed.

REVERSED

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